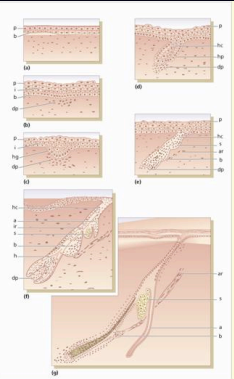


Development of the epidermis, hair follicle and associated structures:

- Section of skin of embryo at about 4 weeks. The periderm (p) is clearly seen, and a basal or germinative layer (b) appears in some areas.
- Skin at about 11 weeks. The epidermis is made up of basal cells, cuboidal in shape (b), and cells of the stratum intermedium (i) are beginning to appear above them. The periderm (p) consists of a single cell layer. Mesenchyme cells (dp) are beginning to aggregate below a presumptive hair follicle.
- Hair germ (hg) stage. Basal cells are now columnar and starting to grow downwards.
- Hair peg (hp) stage. Cells of the so-called "hair canal" (hc) form a solid strand.
- Bulbous hair peg. Note the solid hair canal (hc), sebaceous gland rudiment (s), bulge (b) for attachment of developing arrector muscle (ar).
- Later stages showing apocrine rudiment (a), sebaceous gland (s) now partly differentiated, and bulge (b). The dermal papilla (dp) has been enclosed and a hair (h) is starting to form, with an inner root sheath (ir).
- Complete pilosebaceous unit of axillary skin from a 26-week-old fetus. The sebaceous gland is well differentiated and the apocrine gland (a) is canalized.



Excerpt from "Anatomy and Organization of the Human Skin", Chapter 3, McGrath et al.

Table 3.1 Morphological events during fetal skin development.
(Data from Holbrook and Hoff [8].)

	Month (gestation)					
	1	2	3	4	5	6
Hair peg				+		
Exposed hair					+	
Nail				+		
Sebaceous gland					+	
Apocrine gland						+
Eccrine gland						+
Follicular keratinization					+	
Interfollicular keratinization						+
Non-keratinocytes						
Melanocytes						
Non-functioning			+			
Active				+		
Langerhans' cells				+		
Merkel cells				+		

Development of Skin

Skin

largest organ of the body
protective layer, barrier to the external world (inside-out and outside-in)

2 embryonic origins:

epidermis derives from surface ectoderm

dermis derives from mesoderm (except on the face/head, where dermis derives from ectoderm)

ectoderm/mesoderm interaction form appendages in an inductive manner
between overlying epithelia/underlying mesenchyme

Development of Skin

- * skin has different structures/appendages associated with different regions of the body
- * nails, hair, glands, teeth, eyelashes, eyebrow
- * 2 main types of skin- thin (most of body) thick (soles of feet and hands)
- * week 4-5 single ectodermal layer
- * Epidermis
- * initially periderm
- * keratinization and desquamation
- * replaced by basal cells
- * vernix caseosa
- * covers fetal skin- secretions from sebaceous glands
- * protects skin from extraembryonic fluids amnion, urine
- * slippery and helps with parturition
- * stratum germinativum basal layer week 11 forms intermediate layer
- * periderm then lost replaced by stratum corneum
- * week 10 epidermal ridges are formed by proliferation

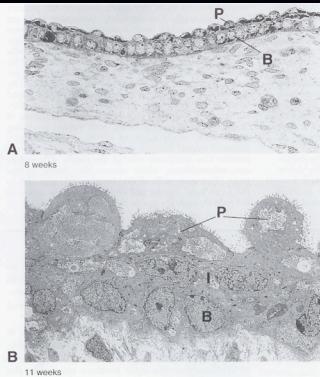
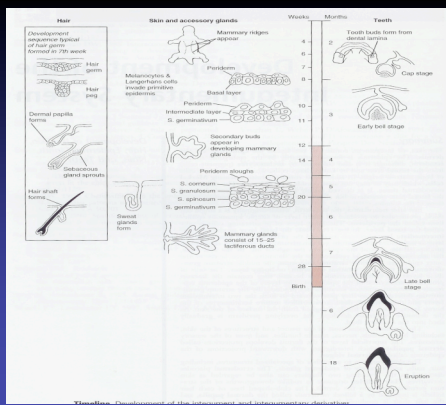
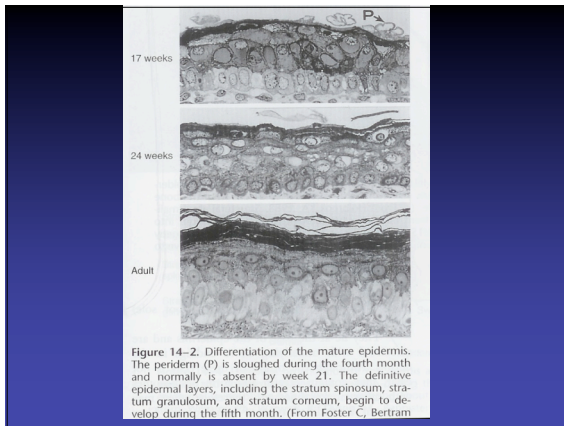


Figure 14-1. Differentiation of the ectoderm into the primitive epidermis. A. Between 8 and 9 weeks, the surface ectoderm has begun to proliferate to form a periderm layer (P). The proliferating layer is now called the basal layer (B). B. By week 11, the basal layer (B) produces an intermediate layer (I) while a complete but irregular outer layer of periderm (P) is still apparent. (From Holbrook KA, Dale BA, Smith LT, et al. 1987. Markers of adult skin expressed in the skin of the first trimester fetus. *Curr Probl Dermatol* 16:94.)



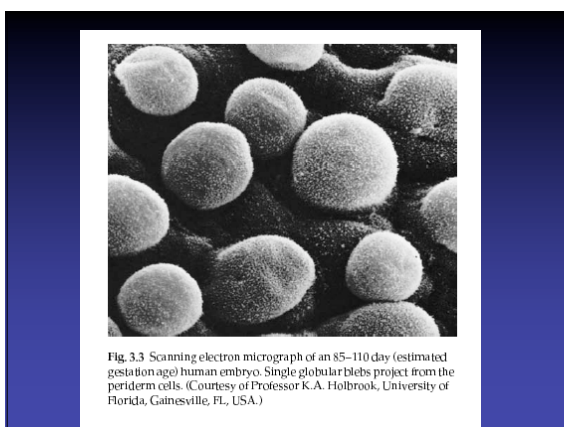
Skin Keratins

- * Keratin
- * large family of intermediate filament protein
- * 17+ isoforms

•Several skin diseases associated with mutations in keratin genes

*Keratins are the major structural proteins of the vertebrate epidermis and its appendages, constituting up to 85% of a fully differentiated keratinocyte.

Together with actin microfilaments and microtubules, keratin filaments make up the cytoskeletons of vertebrate epithelial cells.



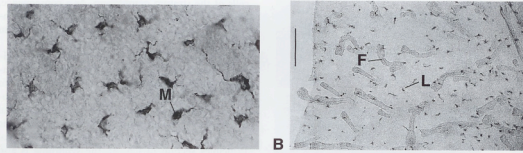


Figure 14-3. Specialized cells of the epidermis. **A.** Melanocytes (M) first appear in the embryonic epidermis during the sixth and seventh weeks. **B.** Langerhans cells (L) migrate into the epidermis from the bone marrow starting in the seventh week. F = hair follicle. (A. From Holbrook KA, 1988. Structural abnormalities of the epidermally derived appendages in skin from patients with ectodermal dysplasia: insight into developmental errors. *Birth Defects Orig Artic Ser* 24:15. B. From Foster C, Holbrook KA, 1989. Ontogeny of Langerhans cells in human embryonic and fetal skin: cell densities and phenotypic expression relative to epidermal growth. *Am J Anat* 184:157.)

Neural crest cells

- * Neural crest cells migrate into skin (late embryonic) to form melanoblasts
- * day 40-50 differentiate into then melanocytes
- * form pigment granules
- * different content of melanin accounts for different skin colors

Dermis and Blood Vessels

- * Dermis
- * lateral plate mesodermal in origin
- * forms connective tissue
- * Blood Vessels
- * week 5 blood vessels form in mesenchyme
- * for capillary beds, extensive remodelling with development

Skin Dermatomes

- * pattern of skin innervation
- * related to original position of limbs prior to rotation
- * dermatome
- * area supplied by single spinal nerve
- * motor and sensory DRG
- * skin supplied by cutaneous nerve

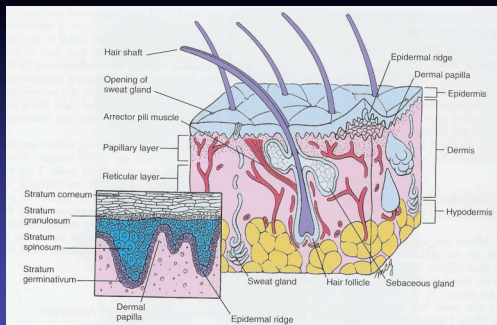
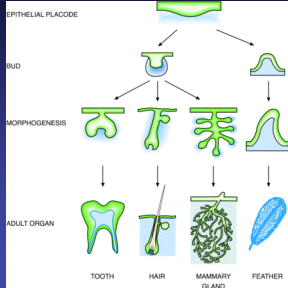


Figure 14-4. Definitive organization of the dermis and epidermis. The patterns of interdigitating dermal papillae and epidermal ridges first develop during the third month. Sebaceous glands develop from the epidermal lining of the hair follicles, appearing about 1 month after a given hair bud is formed. (Modified from Williams PL, Warwick R, Dyson M, Bannister LH, 1989. *Gray's Anatomy*. Churchill Livingstone, Edinburgh.)

Tooth and Hair Development



- Formation of epithelial placode
- Placode buds into or out of mesenchyme
- Mesenchyme directs folding and branching of epithelium during morphogenesis

Pispa and Thesleff 2003

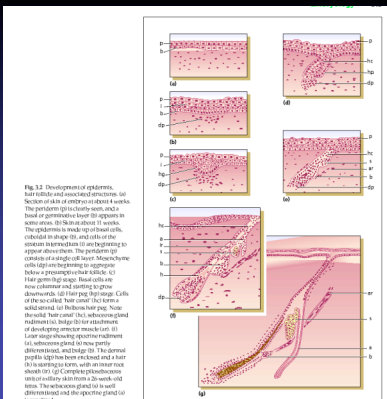
Hair Development

- * week 9-12
- * follicle forms in st. germinativum of epidermis
- * hair bud -> hair bulb
- * hair bulb forms hair
- * mesenchyme forms hair papilla
- * germinal matrix cells become keratinized to form hair shaft
- * week 12 - lanugo hair
- * first hair formed replaced postnatally
- * Function of lanugo hair is to bind vernix to skin

- Regional specificity of hair types
 - Eyebrow, eyelash, scalp, body, pubic/axillary

- * Secondary Hair Development
- * puberty
- * coarse hair in pubis and axilla
- * males face, chest, etc

- * Melanocytes produce melanin which influences hair color
- * arrector pili muscle develops in mesenchyme



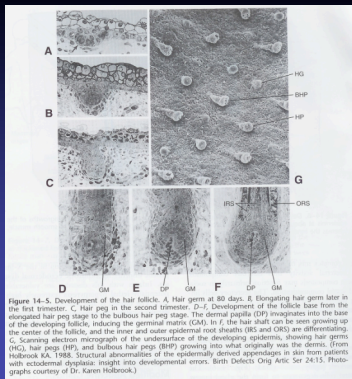


Figure 14-5. Development of the hair follicle. A, Hair germ at 80 days. B, Elongating hair germ later in the first trimester. C, Hair peg in the second trimester. D-E, Development of the follicle base from the elongated hair peg stage to the bulbous hair peg stage. The dermal papilla (DP) invaginates into the base of the developing follicle, inducing the germinal matrix (GM). In F, the hair shaft can be seen growing up the center of the follicle, and the inner and outer epidermal root sheaths (RS and QRS) are differentiating. G, Scanning electron micrograph of the underside of the developing epidermis, showing hair germ (HG), hair peg (HP), and bulbous hair peg (BHP) growing into what originally was the dermis. (From Holbrook KA, 1988. Structural abnormalities of the epidermally derived appendages in skin born patients with ectodermal dysplasia: insight into developmental errors. *Born Defects Orig Assoc Ser* 24:15. Photographs courtesy of Dr. Karen Holbrook.)

Development of Glands

- * 2 main types
- * sebaceous and sweat
- * form as ingrowth of ectoderm into mesoderm

- * sebaceous
- * associated with hair development
- * except on the glans penis and labia minora
- * these glands secrete vernix/sebum

- * sweat glands
- * mostly eccrine, some regional apocrine
- * apocrine in axilla, pubic and nipple regions

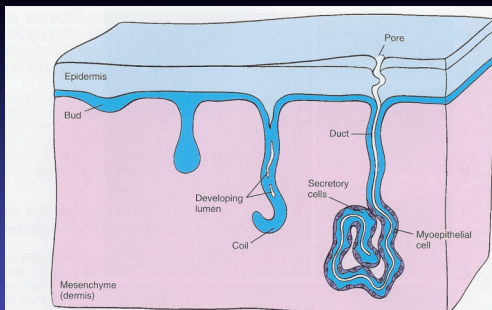
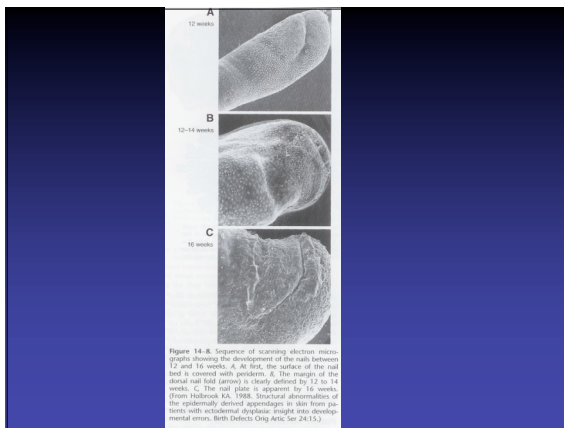


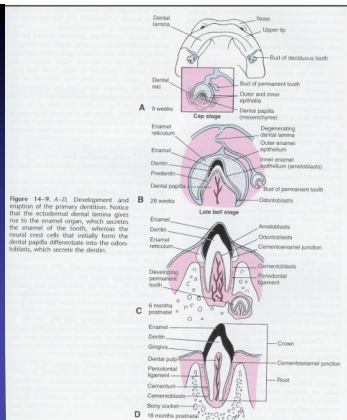
Figure 14-6. Development of sweat glands. Sweat glands first appear as elongated downgrowths of the epidermis at about 20 weeks. The outer cells of the downgrowth develop into a layer of smooth muscle, whereas the inner cells become the secretory cells of the gland.

Nail Development

- * week 10, fingernails develop before toenails
- * same processes as in limb development
- * nail field
- * appears at tip and migrates to dorsal surface
- * thickened epidermis
- * surrounding cells form nail fold
- * keratinization of proximal nail fold forms nail plate
- * nails reach tip
- * week 32 fingernails
- * week 36 toenails
- * nail growth is an indicator of prematurity



Tooth Development



Mammary Glands

- * week 6 epidermis downgrowth into dermis
- * modified sweat glands
- * epithelial/mesenchyme inductive interaction
- * mesenchyme forms connective tissue and fat
- * mammary ridges- mammary bud formation
- * pair of ventral regions axilla to inguinal
- * pectoral regions generate breasts
- * buds branch to form lactiferous ducts
- * only main duct formed at birth
- * Mammary Glands
- * mammary pit
- * forms fetal period
- * depressed region at gland
- * areola
- * proliferation of connective tissue postnatally
- * prior to puberty male and female glands the same
- * Mammary Glands-Puberty
- * sex hormone estrogen stimulate growth
- * full development approx 20 years
- * mainly fat and connective tissue deposition
- * growth also influenced by other hormones
- * progesterone, prolactin, corticoids, growth hormone

Table 3.1 Morphological events during fetal skin development.
(Data from Holbrook and Hoff [8].)

	Month (gestation)					
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Sebaceous gland					+	
Apocrine gland						+
Eccrine gland						+
Follicular keratinization					+	
Interfollicular keratinization						+
<i>Non-keratinocytes</i>						
Melanocytes						
Non-functioning			+			
Active				+		
Langerhans' cells				+		
Merkel cells				+		

Pattern Formation Skin

•Pattern formation in skin development - regional specificity

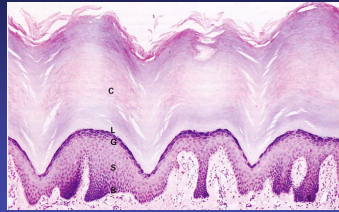
•In birds, the main appendages are the feathers and the foot scales. Their formation results from a series of inductive events between ectoderm (later epidermis) and subectodermal mesoderm (later individualized dermis).

•Morphogenetically, the **mesodermal (mesenchymal)** component of skin is the predominant tissue, insofar as it controls most morphological and physiological features of developing skin and appendages, notably transformation of ectoderm into epidermis, polarization, proliferation and stratification of epidermal cells, initiation, site, size and distribution pattern of epidermal placodes, species-specific architecture of appendages, regional specification of keratin synthesis.

•The **ectodermal (epithelial)** component is able to respond to the mesodermal inductive instructions by building feathers and scales in conformity with the specific origin of the dermis. In these epithelial-mesenchymal interactions, extracellular matrix and the microarchitecture of the dermal-epidermal junction appear to play an important role.

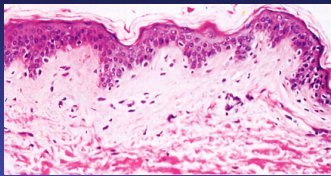
•Extracellular matrix components (primarily collagens, proteoglycans and adhesive glycoproteins) and dermal cell processes close to the epidermal basement membrane become distributed in a microheterogeneous fashion, thus providing a changing substratum for the overlying epidermis. It is assumed that the latter is able to somehow sense the texture and composition of its substratum, and by doing so to appropriately engage in the formation of glabrous, feathered or scaly skin.

EPIDERMIS FROM THICK SKIN



Wheater's Functional Histology

THIN SKIN



Wheater's Functional Histology

STRUCTURE OF THE SKIN

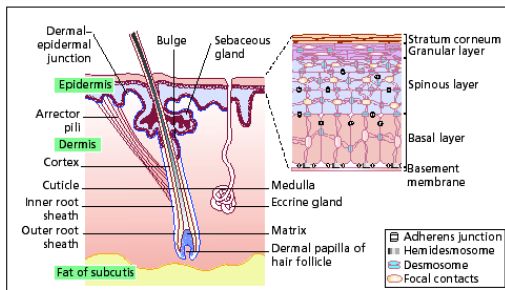
- Epidermis
- Dermis
- Subdermal connective tissue
- Adipose layer

THE SKIN AND ITS CELLS

- Epidermis
 - Keratinocytes
 - Melanocytes
 - Merkel cells
 - Langerhans cells
 - Lymphocytes

THE EPIDERMIS

- Patterns of proliferation and differentiation
- Keratin filaments
- Mechanisms for adhesion
 - Desmosomes
 - Hemidesmosomes
- Disorders of cytoskeleton and adhesive structures



TERMINAL DIFFERENTIATION

The diagram illustrates the process of terminal differentiation in the epidermis. On the left, a histological section shows the epidermal layers: Stratum Corneum, Granular Layer, Spinous Layer, and Basal Layer. On the right, a schematic model shows the same layers with cells at different stages of differentiation. Labels include: Spinous, Stratum Corneum, Granular Layer, Spinous Layer, Basal Layer, and Melanocytes. A legend indicates that K14 is expressed in spinous layers, K5 is expressed only in granular and basal layers, and K1 and K6 are expressed only in the basal layer during wound healing.

TERMINAL DIFFERENTIATION IN EPIDERMIS

Labels in the diagram include:

- Spinous
- Stratum Corneum
- Granular Layer
- Spinous Layer
- Basal Layer
- Melanocytes
- K14 expressed in spinous layers
- K5 expressed only in granular and basal layers
- K1 and K6 expressed only in basal layer during wound healing

Fuchs, E. Mol. Biol. Cell, 8: 189-230 1997



KERATIN FILAMENTS AND EPIDERMAL INTEGRITY

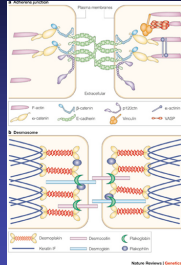


MECHANISM OF EPIDERMAL RENEWAL

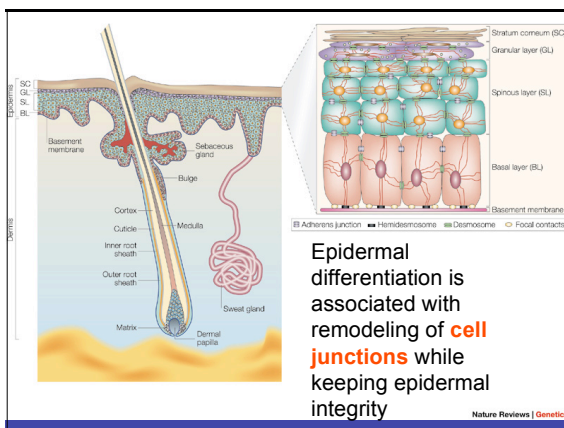
The diagram illustrates the process of epidermal renewal. On the left, a vertical column of blue circles represents the basal layer, with the top one labeled 'KSC'. A curved arrow labeled 'Self renewal' points from the top KSC to the bottom KSC. To the right of this column is a single cyan circle labeled 'CL'. Further right, two yellow circles labeled 'TA' are stacked vertically. To the right of the TA cells are three rows of light blue oval cells labeled 'DIFF'. To the right of the DIFF cells are three rows of light blue rectangular cells, representing the stratum corneum. The label 'Terminal differentiation' is positioned below the TA and DIFF cells.

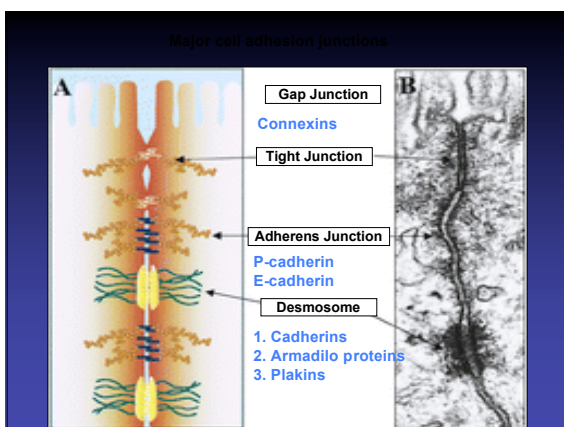


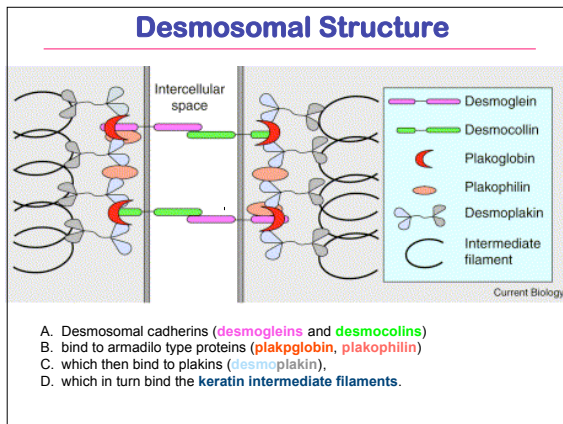
KERATINOCYTE ADHESION

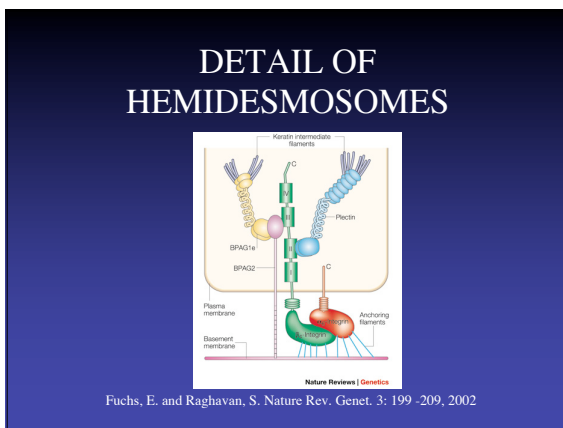


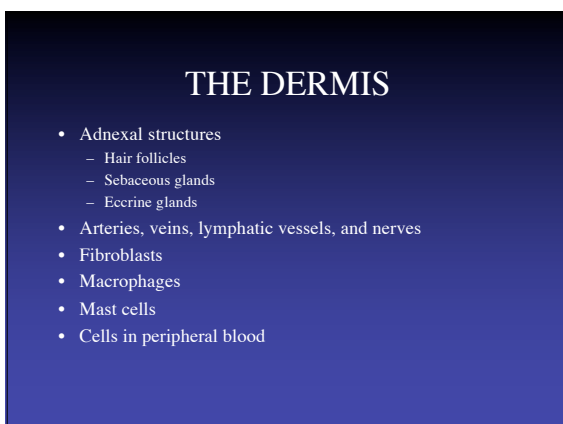
Fuchs, E. and Raghavan, S. Nature Rev. Genet. 3: 199 -209, 2002



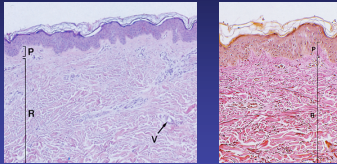








THE DERMIS



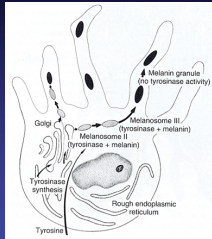
Wheater's Functional Histology

DERMAL FIBERS

- Collagen
 - Type I
 - Type IV (basal laminae)
 - Type V
 - Type VII
- Reticular fibers
 - Type III
- Elastic fibers

FUNCTIONS OF SKIN

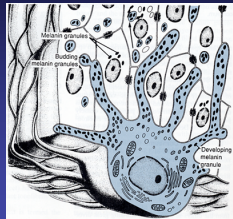
- Protection
- Excretion
- Thermoregulation
- Sensation
- Metabolism
- Immune
- Cosmetic



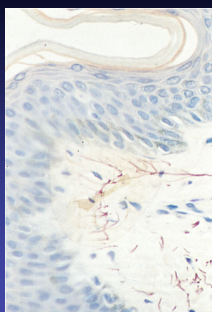
MELANIN SYNTHESIS

Junqueira,
Basic Histology, 1998

CUTANEOUS MELANOCYTE



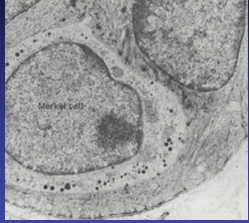
Junqueira, Basic Histology, 1998



FREE NERVE ENDINGS

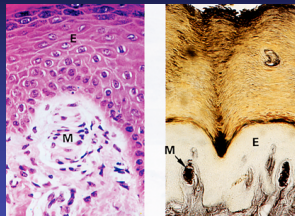
Wheater's Functional Histology

MERKEL CELL

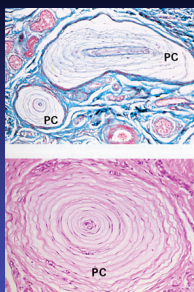


Bloom and Fawcett, Histology

MEISSNER'S CORPUSCLES Light touch receptors



Wheater's Functional Histology



PACINIAN CORPUSCLES: Respond to pressure

Wheater's Functional Histology

LYMPHATIC AND BLOOD CAPILLARY NETWORKS



Skobe, M and Detmar, M.J., Invest. Dermatol. S. 5(1): 14-19, 2000

SUMMARY

Functions of the skin

- Protection - keratinocytes
- Excretion - eccrine and sebaceous glands
- Thermoregulation - blood vessels
- Sensation - nervous elements
- Metabolism - keratinocytes
- Immune function - Langerhans cells

HAIR FOLLICLES: A DEVELOPMENTAL SYSTEM

- Cyclic growth and regression of follicles
- Production of hair-specific keratins
- Differentiation into 8 specific cell types
- Modulation of vasculature
- Modulation of innervation

FUNCTIONS OF HAIR FOLLICLES

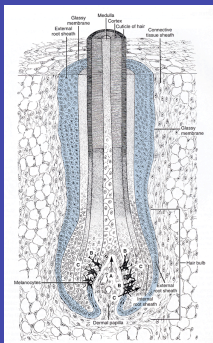
- Form hairs
- Protection: trauma, temperature extremes
- Communication
- Participates in other functions of skin
 - Immune
 - Neural
 - Regenerative



ANAGEN HAIR BULB

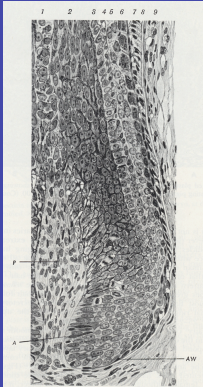
(Masson's Trichrome Stain)

Wheater's Functional Histology



ANAGEN HAIR FOLLICLE

Junqueira Basic Histology

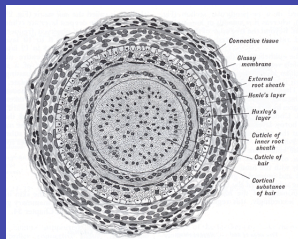


LAYERS OF AN ANAGEN HAIR FOLLICLE

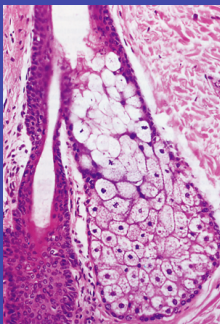
1. Medulla
2. Cortex
3. Hair cuticle
4. Inner root sheath
5. Huxley's layer
6. Henle's layer
7. External root sheath
8. Glassy membrane
9. Connective tissue sheath

Bloom and Fawcett's Histology

LAYERS OF ANAGEN HAIR FOLLICLE (XS)



Bloom and Fawcett's Histology



SEBACEOUS GLAND AND DUCT

Wheater's Functional Histology

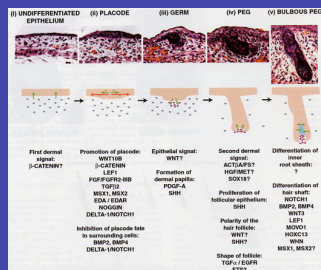
PATTERNING OF HAIR FOLLICLES

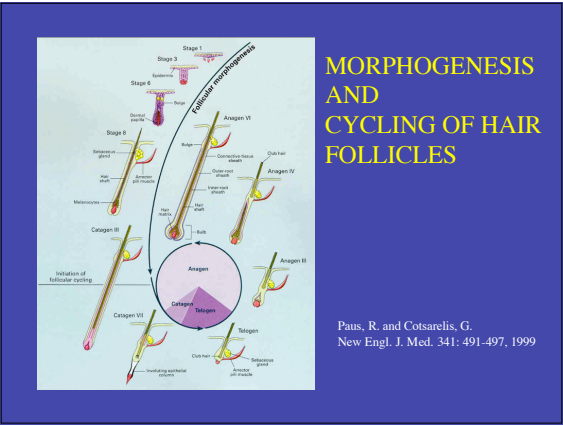
- Follicles are heterogeneous over the body
- Follicular heterogeneity is supported in part by the follicular papilla
- Follicular papillae are sensitive to androgens and estrogens
- Terminal follicles: long, thick, and pigmented
- Vellus follicles: small and unpigmented

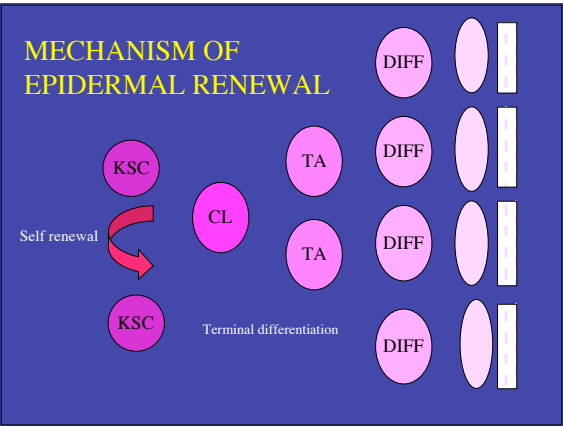
MORPHOGENESIS OF HAIR FOLLICLES

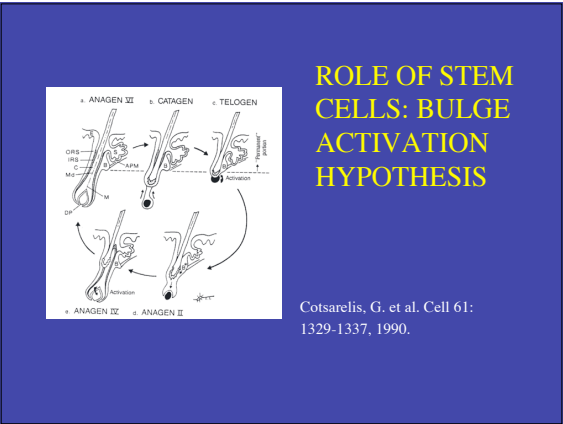
- First dermal signal
- Formation of epithelial placodes
- Epithelial signal from placode
- Formation of dermal condensate
- Second dermal signal
- Downgrowth of epithelial cells
- Differentiation of inner root sheath

MORPHOGENESIS OF HAIR FOLLICLES









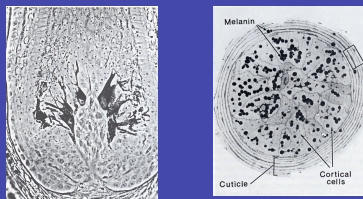
CONTROL OF HAIR GROWTH

- Depends on the stimulus and support of the follicular papilla (growth factors)
- Character of follicular papilla influences size and properties of hair shaft
- Follicular papilla is necessary
 - New hair cycle
 - Normal hair growth

PIGMENTATION OF HAIR FOLLICLES

- Melanocytes originate in the neural crest
- Melanocytes are positioned above follicular papilla in the basal layer of the hair bulb
- Melanocytes become active in early anagen
- Melanocytes die by apoptosis in catagen
- Melanocyte stem cells reside in the bulge

MELANIZATION OF HAIR



Bloom and Fawcett's Histology

Montagna, W. Structure and Function of Skin, 1956

Montagna, W. Structure and Function of Skin, 1956



Telogen	Early anagen	Mid anagen	Late anagen	Catagen	Telogen
---------	-----------------	---------------	----------------	---------	---------



Peters, E.M.J. et al. *J. Invest. Dermatol.* 116: 236-245, 2001.

